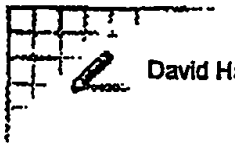

David Haenick

To: aretzios@ribogene.com
cc: Eckhard Bauer/MedAff/RobertsPharm@RobertsPharm, Gloria Lapsley/MedAff/RobertsPharm@RobertsPharm, Michael Petrone/MedAff/RobertsPharm@RobertsPharm

Subject: Emitasol Phase III Protocol

Dear Anastassios,

Thank you for your thoughtful review of the protocol. Your comments and suggestions were taken under consideration very seriously. We have also met internally and discussed with you our thoughts over the course of the review. We also appreciate the time and effort taken by GloboMax in this process. Since critical times are approaching, we need to bring the protocol review process to closure. Accordingly, we have decided on the following recommendations to GloboMax for 5 key issues :

1. retain the PK/PD analysis in the protocol while clarifying that only the analytical site is unblinded.

2. do not change the

3. keep the

4. keep the current patient global assessment (5-point scale)

5. keep the cardinal symptom score analysis in the protocol

Also, other changes to the protocol were made per your request.

Please read GloboMax's latest response to items 1-4, which I will be sending by fax.

Kind regards,

David

Comment #38 PK Response:

The pharmacokinetic data that will be collected in the phase II PK study will allow characterization of the pharmacokinetics in this target population. However, it will not enable us to determine the influence of covariate effects, such as age, race, gender, creatinine clearance, etc, on these parameters. This will only be possible by conducting an analysis combining the data from the phase III study in addition to the information from the phase II study. The agency requires estimation of the pharmacokinetic parameters and the influence and relationship of covariate effects in the patient population on these parameters. This information will be important for approval and for the label for this indication. (It is also important to remember that little or no information with regards to the pharmacokinetics of the oral formulation of this drug in this patient population is available). With regards to the validity of combining pharmacokinetic data from many studies using the population approach, please see the attached FDA guidance. In addition, we have been involved in several studies or have knowledge of studies that were submitted as part of an approved NDA such as that included data from multiple studies as part of the PK and PK/PD analyses.

Determination of the plasma concentrations potentially unblinding this study is also not an issue. Normal practice is to unblind the bioanalytical site, so that placebo samples would not be analyzed. The bioanalytical site would sign a statement to state that no information would be forwarded to any persons until the sponsor notifies them. We potentially have two options with regards to the timing of the unblinding of the bioanalytical site so that sample analysis can occur. These options are:

a) Unblind the bioanalytical site during the course of the study so that samples can be analyzed on an ongoing basis, and results will not be released until the sponsor authorizes this, which will occur sometime after the last CRF is signed off.
b) Unblind the bioanalytical site after the last CRF is signed off, so that samples can be analyzed in one batch job at the end of the study. Again, the results will not be released until the sponsor authorizes this.

Both of these options are normal practice in phase III studies in which pharmacokinetic samples are collected. A major consideration for Roberts in determining which option to choose (a) or (b) will be the impact that the choice will have on the timelines.

Comment #4 Primary Efficacy Endpoint Response

In the protocol that was submitted to the FDA, the mean change in the symptom score of 3.5 was used in the power calculation. The FDA did not comment on our use of 3.5 in the power calculations because they felt that the sample size was reasonable, not because they believed that a difference in means of 3.5 points was clinically

significant. Some protocols will have a clinically relevant change for an individual patient, but generally not for the overall results. We believe that the primary consideration for approval (with regard to effectiveness) for the emitasol product is to achieve a statistically significant result with the primary endpoint, using the primary analysis specified in the protocol. Even if we were to state 3.5 points to be our definition of a clinically significant difference in means in the protocol, the FDA would not necessarily be bound to it. We also have the additional risk of the study resulting in a mean change that would be less than 3.5. This would then be considered a failed study, even if we have statistical significance. Similarly, if the difference in means is 3.7 and the p-value > 0.05 the FDA would not approve the drug, even if we had declared 3.5 to be a clinically significant difference in means in the protocol. We would recommend that the number related to clinical significance not be defined in the protocol. Once the study is completed, we will defend the change in symptom scores as being clinically significant, whatever that number happens to be. If this product was a new class of an NCE, an advisory committee would probably be convened to discuss this issue, but in this case the FDA reviewers will consider the results and discussion as part of the normal approval process. We believe that this pathway

Comment #9 Screening:

The 28 day screening period is not a mandatory period of time applied to all subjects. This period is only included to set a time limit for the validity of the clinical laboratory assessments and that are obtained during this time. If the investigator only needs 1 day to obtain all the assessments and the patient does not require a washout period, that patient can be entered into the study the next day. As you know, setting a time limit on the screening period is a standard clinical procedure, but by extending this to 28 days it decreases the likelihood of having to repeat laboratory assessments if there was some delay in entering the patient into the study. This would also result in decreased cost.

Comment #24 Global Assessment Response

At our joint meeting with Roberts we discussed the virtues of a responder analysis versus that of a global assessment. In trying to establish a responder definition we found no way to do this that was more than an arbitrary assignment of a numeric response. Given the current status of measurement of the symptoms of diabetic gastroparesis, there is no data available to provide guidance for a validated numeric estimation of response. When we sought the advice of our expert consultants, they were unanimously in favor of a 5-point categorical global assessment. We, therefore, felt that a measure somewhat independent of the primary endpoint would be of more value than an arbitrary score. Other options for this assessment would be to use a quality of life assessment score as they did in the Domperidone study, or some other summary value questionnaire. Using the QOL from the Domperidone study however would be more time consuming, and would allow the FDA to further question responses to individual questions in the symptomology assessment. For the

evaluation of a secondary endpoint, any of these options of assessment would be acceptable.

Subjective Endpoint as a PD endpoint:
Ribogene disagrees with using a subjective endpoint (change in total symptom score) as a PD endpoint.

A questionnaire score and it's change during the study is a commonly used as a PD measure in diseases where surrogate markers are not well established or no 'objective' clinical endpoints exist. We have submitted and seen numerous examples of this type of endpoint included in NDA submissions. Some examples of this are with analgesic trials, where a pain relief score is used as a PD measurement [1,2,3].

1. Sheiner L, Beal S. Dunne A. (1997) Analysis of nonrandomly censored ordered categorical longitudinal data from analgesic trials. JASA 92(440): 1235-1244
2. Mandema J, Stanski D. (1996) Population pharmacodynamic model for ketorolac analgesia. CPT 60(6): 619-635
3. Liu C.Y., Sambol N. (1995) Pharmacodynamic analysis of analgesic trials using empirical methods. Pharm. Res. 12(3): 438-445